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Hepatitis in early syphilis
Report of three cases

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SUMMARY Fifteen patients with early syphilis were seen between May 1974 and March 1975. These 15 patients comprised all the cases of early syphilis that were seen in Edinburgh during this period. Three of them were men of whom two were homosexual. Liver function tests in these three gave abnormal results.

Introduction

As part of a widespread treponemal dissemination, a diffuse hepatitis occurs in congenital syphilis, and a pericellular cirrhosis may result (Flegel, 1951). Liver disease in patients suffering from acquired early syphilis is uncommon, and it is still not known if *Treponema pallidum* or some other agent is responsible for the hepatic dysfunction (Sherlock, 1968). Hahn (1943) found 80 cases of hepatitis in nearly 34 000 cases of early syphilis. Some of these patients had received arsphenamine treatment before investigation and it is difficult to decide whether liver damage was a result of the infection or the treatment. Since then the incidence of syphilis has decreased and case reports of liver disease associated with syphilis have appeared only intermittently.

The following is an account of three patients with early syphilis and liver dysfunction. None was known to have had contact with hepatitis.

CASE 1

A 38-year-old White man, a gardener, was admitted to the City Hospital, Edinburgh, in May 1974. He complained of generalised itch, malaise, anorexia, nausea, intermittent fever, dark urine, and vague right upper abdominal pain of five days' duration. On the day of admission he noticed a yellow tinge to the sclera. There was no recent history of drug or alcohol abuse, injections or transfusions, and he had not been abroad. He had been seen two months previously at the Department of Venereology, Royal Infirmary, Edinburgh, as a contact of a case of primary syphilis. At that time examination, including proctoscopy, had been normal. His Venereal Diseases Research Laboratory (VDRL) and *Treponema pallidum* haemagglutination (TPHA) tests had given negative results.

On admission the patient was afebrile and jaundiced. Discrete, non-tender, firm, mobile lymph nodes were palpable in the cervical, axillary, and inguinal regions. An enlarged, smooth tender liver extended 4 cm below the right costal margin. The spleen was not palpable. There was no evidence of a healed primary lesion on the genitalia, the anorectum, or in the mouth, and there was no rash.

The haemoglobin (Hb) was 14.2 g/dl white cell count (WCC) $9{\cdot}8 \times 10^9$/l with a normal differential count. The prothrombin time was 14 seconds (normal) and the erythrocyte sedimentation rate (ESR) was 80 mm in the first hour (Westergren). The urine contained a trace of urobilinogen, but no bilirubin. The serum bilirubin was 50 μmol/l (normal 3–14), the alanine aminotransferase was 182 units/l (normal 5–41), and the alkaline phosphatase 523 units/l (normal 20–85). Antismooth muscle and antimitochondrial antibody tests were negative. Two blood cultures taken on admission were sterile. There was no evidence, by serological testing of paired sera, of infection with *Leptospira* species, Epstein-Barr (EB) virus, or cytomegalovirus. The Paul Bunnell test gave negative results. Hepatitis-B antigen tested after fivefold serum concentration by gel diffusion was negative.

The VDRL titre was positive at 1:8, TPHA positive at 1:80, and the fluorescent treponemal antibody absorption (FTA-ABS) test was also positive.

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Four days after admission he developed a maculopapular rash on the trunk and on the soles of his feet. Intravenous cholangiography performed six days after admission failed to outline the biliary system. Another examination 23 days later showed faint opacification of the gall bladder and bile ducts, which appeared normal.

The patient was treated with 1 megaunit of benzyl penicillin intramuscularly, eight hourly for the first three days, followed by 900 000 international units (iu) of procaine penicillin daily for another 11 days. Six hours after the first injection his axillary temperature rose to 39.6°C and he developed rigors and an exacerbation of his abdominal pain. The rash became more erythematous and extensive. The pyrexia subsided after six hours.

The rash had faded considerably after one week and his jaundice disappeared after two weeks. He continued to complain of generalised pruritus two months later. He was unable to attend again.

CASE 2

A 22-year-old man, a hotel manager, attended the Department of Venereology, Royal Infirmary, Edinburgh, in April 1976. He complained of a non-pruritic rash on his penis for 10 days. Apparently he had had homosexual contact three months previously. There was no other relevant history. He drank alcohol rarely and there was no history of recent drug abuse, vaccination, tattooing, or blood transfusion.

Examination showed a papulosquamous rash on his neck, chest, back, abdomen, scrotum, penis, and thighs. Typical condylomata lata were noted in the perianal region. There was painless enlargement of the cervical, axillary, inguinal and epitrochlear lymph nodes, but neither the liver nor spleen was palpable. No evidence of a healed primary lesion was found on the genitalia, mouth, pharynx, or in the anal canal. There was no jaundice, the urine showed a trace of urobilinogen, but no bilirubin.

Darkground examination of exudate from the condylomata lata revealed typical *T.pallidum*. The VDRL test gave positive results at 1:32, the TPHA test was 1:5120, and the FTA-ABS test also gave positive results.

Hb was 15·2 g/dl, the WCC $10{\cdot}8 \times 10^9$/l. Serum bilirubin was 12 μmol/l, alanine aminotransferase 189 iu per litre, alkaline phosphatase 520 iu per litre—the isoenzymes of the last chiefly being of liver origin.

Haemagglutination test for hepatitis-B surface antigen, and radioimmunoassay for antibody to hepatitis B surface antigen were negative. Paul Bunnell test was negative and there was no evidence, on serological testing of paired sera, of infection with *Brucella* sp., *Leptospira* sp., *Herpes simplex* virus, measles, mumps, Q-fever, *Mycoplasma pneumoniae*, *psittacosis*, or *Toxoplasma*.

Rheumatoid factor was not detected in the serum, nor were antinuclear factor, antismooth muscle antibody, or antimitochondrial antibody.

Six hours after an intial injection of procaine penicillin (1 megaunit) the patient's temperature rose to 39°C and he felt unwell. During and after this presumed Herxheimer reaction there was no evidence of jaundice. His treatment with 1 megaunit of procaine penicillin was continued as a daily injection for 14 days.

Fourteen days after starting treatment, his serum bilirubin was 10 μmol/l, alanine aminotransferase 47 iu per litre, and alkaline phosphatase 303 iu per litre. By the third week after starting treatment, the bilirubin was 11 μmol/l, alanine aminotransferase 27 iu per litre, and alkaline phosphatase 207 iu per litre. When reviewed six weeks later, he was asymptomatic and there were no abnormal clinical findings. His liver function tests all gave normal results.

CASE 3

A 46-year-old businessman who had had sexual intercourse with a prostitute some eight weeks previously, attended the Department of Venereology, Royal Infirmary, Edinburgh in March 1975, when he complained of a painless penile ulcer for two weeks. Examination showed a non-tender, indurated ulcer on the glans penis with bilateral inguinal lymph node enlargement. There was no evidence of jaundice or mucocutaneous lesions of secondary syphilis. The liver was not enlarged.

Darkground examination of exudate from the penile lesion revealed typical *T. pallidum*. The serum VDRL test gave positive results at 1:8, the TPHA test negative results, while those for FTA-ABS test were positive. Serum alkaline phosphatase was 780 iu per litre, and the isoenzymes were of liver origin. The serum alanine aminotransferase was 240 iu per litre, the bilirubin 15 μmol/l, the total plasma protein 78 g/l, and the serum albumin 35 g/l.

A diagnosis of primary syphilis was made and he was treated with penicillin triple injection (Triplopen) 1·25 megaunits daily for 10 days. Six hours after the first injection his temperature rose to 39°C and his pulse rate increased to 130 per minute. During this Herxheimer reaction he had no rash or jaundice, and his liver did not become palpable.

Eight weeks later, he was symptom-free and no abnormal findings were noted on clinical examination. His liver function tests had normal results.

Discussion

The diagnosis of hepatitis in Case 1 was made on the

basis of jaundice, pruritus, hepatic enlargement, and abnormal results of liver function tests. Although there was no clinical evidence of jaundice in Cases 2 and 3, the results of biochemical tests indicated hepatic dysfunction.

Of 15 patients suffering from early syphilis who attended the Department of Venereology, Royal Infirmary, Edinburgh, between January 1974 and June 1976, only the above patients had either clinical or biochemical evidence of liver disease.

Probably the most common type of hepatitis in young adults is viral and it has recently been shown that there is an increased incidence of hepatitis-B among homosexual patients (Heathcote and Sherlock, 1973; Vahrman, 1973). Two of our patients had had several homosexual contacts, but neither hepatitis-B antigen nor antibody was detected in their sera.

The occurrence of a disproportionately high alkaline phosphatase is unusual in viral hepatitis, unless complicated by prolonged cholestasis. A greatly elevated serum alkaline phosphatase level associated with only a moderate increase in alanine aminotransferase level has previously been noted in hepatitis occurring in patients with early syphilis (McCracken *et al.*, 1969; Baker *et al.*, 1971; Lee *et al.*, 1971; Parker, 1972; Sobel and Wolf, 1972).

Fehér *et al.* (1975), in a review of 17 cases of liver disease associated with syphilis, found an elevated alkaline phosphatase in only two patients. Most case reports have stated that the biochemical tests of liver function have returned to normal within two months of treatment, and this was also noted in Cases 2 and 3. However, liver function tests in the first patient were still abnormal at the end of two months. Although viral hepatitis could not be entirely ruled out as a possible cause of liver disease in the patients described, the biochemical findings suggested some alternative aetiology.

The alcohol consumption of the above patients was negligible and there was no history of drug use or abuse. Several hepatoxic agents are used in horticulture, but the first patient, a gardener, had had no contact with such chemicals.

Infectious mononucleosis is a well documented cause of hepatitis (Hoagland and McCluskey, 1955). This disease is common in young adults, but was excluded in Cases 1 and 2 as the aetiological factor by serological investigations.

The results of liver function tests in Case 1 suggested cholestasis and to exclude extrahepatic obstructive jaundice, an intravenous cholangiogram was performed. This failed to demonstrate the biliary system, but another examination two weeks after penicillin treatment gave normal results. Similar findings were described by Sobel and Wolf (1972).

Primary biliary cirrhosis was excluded by the clinical course of the disease and the absence of antimitochondrial antibody, which is present in almost every case of this disease (Doniach *et al.*, 1966). From the pattern of the disease process and the absence of antismooth muscle antibody, active chronic hepatitis was considered to be unlikely.

Liver biopsies have been performed in several cases reported in the literature and although the histological findings are generally stated to be non-specific (McCracken *et al.*, 1969), Fehér *et al.* (1975) suggest that changes occur which are characteristic of early syphilis. Fehér *et al.* (1975) however, based their diagnosis of syphilis on the results of the VDRL and Kölmer tests and by demonstrating treponemes in local lesions in an unknown number of patients. It is uncertain, therefore, if all their cases were infected with syphilis, or whether some of the positive serological tests were biological false positive results. In view of the benign course and response to treatment in most cases reported, it was felt that liver biopsy was not indicated in the acute stage of the illness in the above cases. However, the persistently high level of alkaline phosphatase and continuing pruritus in Case 1 suggested continuing liver disease and had the patient not defaulted, liver biopsy would have been justified.

Syphilis is a systemic disease and treponemes may be expected to reach the liver. Fehér *et al.* (1975) demonstrated organisms resembling treponemes in liver biopsies of seven cases of syphilis associated with hepatitis. It is uncertain however, whether they produce cell damage, or induce an autoimmune hepatitis.

The above case reports emphasise the difficulties entailed in incriminating syphilis as the cause of hepatitis. They do indicate the need to exclude syphilis when the liver function tests of a jaundiced patient do not conform to any well-defined pattern.

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References

Baker, A. L., Kaplan, M. M., Wolfe, H. J., and McGowan, J. A. (1971). Liver disease associated with early syphilis. *New England Journal of Medicine*, **284**, 1422–1423.

Doniach, D., Roitt, I. M., Walker, J. G., and Sherlock, S. (1966). Tissue antibodies in primary biliary cirrhosis, active chronic (lupoid) hepatitis, cryptogenic cirrhosis and other liver diseases, and their clinical implications. *Clinical and Experimental Immunology*, **1**, 237–262.

Fehér, J., Somogyi, T., Timmer, M., and Józsa, L. (1975). Early syphilitic hepatitis. *Lancet*, **2**, 896–899.

Flegel, H. (1951). Uber die Leberveränderungen bei der Lues connata. *Zentralblatt für allgemeine Pathologie und pathologische Anatomie*, **87**, 302–314.

Hahn, R. D. (1943). Syphilis of liver. *American Journal of Syphilis, Gonorrhea, and Venereal Diseases*, **27**, 529–562.

Heathcote, J., and Sherlock, S. (1973). Spread of acute type-B hepatitis in London. *Lancet*, **1**, 1468–1470.

Hoagland, R. J., and McCluskey, R. T. (1955). Hepatitis in mononucleosis. *Annals of Internal Medicine*, **43**, 1019–1030.

Lee, R. V., Thornton, G. F., and Conn, H. O. (1971). Liver disease associated with secondary syphilis. *New England Journal of Medicine*, **284**, 1423–1425.

McCracken, J. D., Hall, W. H., and Pierce, H. I. (1969). Nephrotic syndrome and acute hepatitis in secondary syphilis. *Military Medicine*, **134**, 682–686.

Parker, J. D. J. (1972). Uncommon complications of early syphilis: Hepatitis, periostitis, iritis with papillitis, and meningitis. *British Journal of Venereal Diseases*, **48**, 32–36.

Sherlock, J. (1968). *Disease of the Liver and Biliary System*, p.607. Blackwell: Oxford.

Sobel, H. J., and Wolf, E. H. (1972). Liver involvement in early syphilis. *Archives of Pathology*, **93**, 565–568.

Vahrman, J. (1973). Letter: Spread of acute type-B hepatitis in London. *Lancet*, **2**, 157.